## FATENT COOPERATION TRE. . Y

Mark Dir

X	From the INTERNATIONAL BUREAU
PCT	To:
NOTIFICATION OF ELECTION  (PCT Rule 61.2)	United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ÉTATS-UNIS D'AMÉRIQUE
Date of mailing (day/month/year) 29 January 1999 (29.01.99)	in its capacity as elected Office
International application No. PCT/SE98/00907	Applicant's or agent's file reference J 1747-1 WO
International filing date (day/month/year) 15 May 1998 (15.05.98)	Priority date (day/month/year) 30 May 1997 (30.05.97)
Applicant NYQVIST, Håkan et al	
in a notice effecting later election filed with the Inte	r 1998 (17.12.98)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Nicola Wolff

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

### PATENT COOPERATION TREATY

# **PCT**

		SEP	1999	
WIP	)	F	CT	

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  J 1747-1 WO	FOR FURTHER ACTION	See Notification of Tr Preliminary Examination Re	ansmittal of International
International application No.	International filing date (day/mo		
PCT/SE98/00907	15.05.1998	30.05.19	· · · · · ·
International Patent Classification (IPC)	<del></del>	130.03.13	
C 07 D 311/58, A 61 F	-		
Applicant Astra Aktiebolag et a	al		
This international preliminary ex- Authority and is transmitted to the	amination report has been prepared ne applicant according to Article 36	by this International Prelimina	ary Examining
2. This REPORT consists of a total	of 4 sheets, include	ng this cover sheet.	
been amended and are the	anied by ANNEXES, i.e., sheets of basis for this report and/or sheets on 607 of the Administrative Instruc	ontaining rectifications made b	efore this Authority
These annexes consist of a total of	of 4 sheets.		RECEIVED
3. This report contains indications re	elating to the following items:		NON 1 5 1233
I Basis of the report			TECH CENTER 1600/29
II Priority			1EOU.
III Non-establishment o	of opinion with regard to novelty, in	ventive step and industrial app	olicability
IV Lack of unity of inve	ention		
V Reasoned statement and explanations sup	under Article 35(2) with regard to poorting such statement	novelty, inventive step or indu	strial applicability, citations
VI Certain documents o	ited		
VII Certain defects in the	e international application		
VIII Certain observations	on the international application		
Date of submission of the demand	Date of	completion of this report	
17.12.1998	30.0	8.1999	
Name and mailing address of the IPEA/S		zed officer	
Fatent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667, 72, 88		n Karlsson/Els	

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE98/00907

L Basis of tl	he report			
1. This report under Article	has been drawn or 14 are referred to 11	n the basis of (Replacement she in this report as "originally filed"	zets which have been furnished t " and are not annexed to the rep	to the receiving Office in response to an invitation port since they do not contain amendments.):
	the international	application as originally file	æd.	REC'D 2 2 SEP 1999
$\boxtimes$	the description,	pages 1-9	, as originally filed,	WIDO
		pages	, filed with the demand,	WIPO PCT
			, filed with the letter of	,
		pages	, filed with the letter of	
$\boxtimes$	the claims.	Nos.	, as originally filed,	
			, as amended under Article	<b>2</b> 19,
		Nos.	, filed with the demand,	
			•	17.09.1998
		Nos.	, filed with the letter of	
$\boxtimes$	the drawings,	sheets/fig 1-2	, as originally filed,	
		sheets/fig	, filed with the demand	
		sheets/fig	, filed with the letter of	,
		sheets/fig	, filed with the letter of	
	the description, the claims, the drawings,	Nos. sheets/fig	·	
3. This beyo	report has been es and the disclosure	stablished as if (some of) the as filed, as indicated in the su	amendments had not been n upplemental Box (Rule 70.2)	nade, since they have been considered to go (c)).
4. Additional of	observations, if ne	ecessary:		

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE98/00907

IIL No	on-establishment of opinion with regard to novelty, inventive step and industrial applic	ability
The que	stions whether the claimed invention appears to be novel, to involve an inventive step (to be sle have not been examined in respect of:	non obvious), or to be industrially
	the entire international application,	
$\boxtimes$	claims Nos. 11-14	
because		
$\square$	the said international application, or the said claims Nos. $11-14$	
لاعا	relate to the following subject matter which does not require an international preliminary of	examination (specify):
	thod for treatment of the human or animal body Rule $67.1(iv)$ ).	by therapy
	the description, claims or drawings (indicate particular elements below) or said claims No	S
	are so unclear that no meaningful opinion could be formed (specify ):	
	the claims, or said claims Nos.	are so inadequately supported
	by the description that no meaningful opinion could be formed.	-
	no international search report has been establised for said claims Nos.	

#### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE98/00907

V.	Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
	citations and explanations supporting such statement

I.	Statement			
	Novelty (N)	Claims Claims	1-10,15-17	YES NO
	Inventive step (IS)	Claims Claims	1-10,15-17	YES NO

Industrial applicability (IA) Claims 1-10, 15-17 YES

Claims

#### 2. Citations and explanations

The invention relates to a salt (R)-3-N, N-diclobutylamino-8-fluoro-3, 4-dihydro-2H-1-benzopyran-5-carboxamide hydrogen <math>(2R,3R)-tartate, processes for the manufacture of the salt, and pharmaceutical formulations for treatment of CNS disorders.

No relevant prior art has been found.

WO, A, 9511891 discloses the general state of the art, but is not considered to hinder a patent.

Therefore, the 17-09-1998 amended claims 1-10 and 15-17 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

### PATENT COOPERATION TREATY

**08** -02- 1999

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PCT

From the INTERNATIONAL BUREAU

To:

NOTIFICATION CONCERNING AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and Administrative Instructions, Section 417)

Swedish Patent Office P.O. Box 5055 Valhallavagen 136 S-102 42 Stockholm SUÈDE

Date of mailing (day/month/year) 29 January 1999 (29.01.99)

in its capacity as International Preliminary Examining Authority

International application No. PCT/SE98/00907

International filing date (day/month/year)
15 May 1998 (15.05.98)

**Applicant** 

ASTRA AKTIEBOLAG et al

The International Bureau hereby transmits a copy of the amendments to the claims under Article 19 together with any accompanying statement (Rule 62).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland **Authorized officer** 

Nicola Wolff

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38



WIPO World Intellectual Property Organization 34, Chemin des Colombettes CH-1211 GENEVE 20 Schweiz

September 14, 1998

Our ref. J 1747-1 WO



BY REGISTERED MAIL

Re: PCT/SE98/00907

With reference to PCT Article 19 and Rule 46 the applicant herewith files a new set of amended claims to be published together with the application.

Claim 1 in the originally filed International patent application has been deleted. In consequence the subsequent claims have been renumbered. The reason for the cancellation of the originally filed claim 1 is that said claim 1 has no correspondence in the priority application.

Please acknowledge receipt of this letter by return fax.

Astra AB

Britta Samuelsson

e-mail: britta.samuelsson@astra.se.astra.com

#### **CLAIMS**

- 1. A salt (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5carboxamide hydrogen (2R,3R)-tartrate.
  - The salt (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate monohydrate.
- 10 3. The salt according to any one of claims 1 to 2 in substantially crystalline form.
  - 4. A pharmaceutical formulation containing, as active ingredient, the salt according to any one of claims 1 to 3 in association with a suitable diluent, excipient or an inert carrier.
- A pharmaceutical formulation according to claim 4 for oral administration.
  - 6. The salt according to any one of claims 1 to 3 for use in therapy.
- 7. The use of the salt according to any one of claims 1 to 3 in the manufacture of a medicament in the prevention or in the treatment of CNS disorders and related medical disturbances.
- The use according to claim 7 in the manufacture of a medicament in prevention or in the treatment of 5-HT<sub>1A</sub> receptor antagonist activity related CNS disorders and medical disturbances.
  - 9. The use according to claim 8 in the manufacture of a medicament in the prevention or in the treatment of depression.
- The use according to claim 8 in the manufacture of a medicament in the prevention or in the treatment of anxiety.
- A method for the prevention or the treatment of CNS disorders and related medical disturbances comprising administration, to a host in need of such treatment, an effective amount of the salt according to any one of claims 1 to 3.

- 12. A method according to claim 11 for prevention or the treatment of 5-HT<sub>1A</sub> receptor antagonist activity related CNS disorders and medical disturbances.
- 13. A method according to claim 12 for the prevention or the treatment of depression.
- 14. A method according to claim 12 for the prevention or the treatment of anxiety.
- 15. A process for the manufacture of the salt as defined in any one of claims 1 to 3 characterized by the following consecutive steps:
  - i) dissolving (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1benzopyran-5-carboxamide in an appropriate solvent, optionally by heating,
  - ii) adding (2R, 3R)-tartaric acid, respectively, dissolved in an appropriate aqueous organic solvent or non-aqueous organic solvent,
  - iii) allowing the solution obtained to stand cold to crystallize,
  - iv) optionally recrystallizing in an appropriate aqueous organic solvent, if a non-aqueous organic solvent is used in step ii), to obtain the salt defined in any one of claims 2 or 3.
- 16. A process for the manufacture of the salt as defined in claims 2 to 3 characterized by recrystallizing (R)-3-N,N-dicyclobutylamino-8-fluoro-3, 4-dihydro-2H-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate in an appropriate aqueous organic solvent.
- 17. A process according to any one of the claims 15 or 16, wherein the aqueous organic solvent is aqueous acetone.

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## REQUEST

For receiving Office use only	
International Application No.	
International Filing Date	
Name of receiving Office and "PCT International Application"	

international application be processed according to the Patent Cooperation Treaty.  Name of receiving Office and "PCT International Application and "PCT Internation and "PCT Internatio			
decoroning to the rations cooperation receipt	Applicant's or agent's file reference		
	(if desired) (12 characters maximum) J 1747-1 WO		
Box No. I TITLE OF INVENTION			
A NEW SALT			
Box No. II APPLICANT			
Name and address: (Family name followed by given name; for a legal e The address must include postal code and name of country. The country o Box is the applicant's State (i.e. country) of residence if no State of reside	ntiry, full official designation.  f the address indicated in this ence is indicated below.)  This person is also inventor.		
ASTRA AKTIEBOLAG	Telephone No.		
S-151 85 Södertälje Sweden	+46 8 553 260 00		
	Facsimile No. +46 8 553 288 20		
	Teleprinter No.		
	retepriner 10.		
State (i.e. country) of nationality: SE	State (i.e. country) of residence:		
This person is applicant for the purposes of:  all designated States all designated the United S	d States except the United States the States indicated in the Supplemental Box		
Box No. III FURTHER APPLICANT(S) AND/OR (FURT			
Name and address: (Family name followed by given name; for a legal e The address must include postal code and name of country. The country of Box is the applicant's State (i.e. country) of residence if no State of reside NYQVIST, Håkan Astra Arcus AB S-151 85 Södertälje Sweden	This person is:  applicant only  applicant and inventor  inventor only (If this check-box is marked, do not fill in below.)		
State (i.e. country) of nationality:  SE	State (i.e. country) of residence:		
This person is applicant all designated all designate for the purposes of:	the United States the States indicated in the Supplemental Box		
Further applicants and/or (further) inventors are indicated	on a continuation sheet.		
Box No. IV AGENT OR COMMON REPRESENTATIVE	; OR ADDRESS FOR CORRESPONDENCE		
The person identified below is hereby/has been appointed to act of the applicant(s) before the competent International Authorities	on behalf agent common representative		
Name and address: (Family name followed by given name; for a legal of The address must include postal code and name of Patent Department	entity, full official designation.  Telephone No.  +46 8 553 260 00		
Astra Aktiebolag	Facsimile No.		
S-151 85 Södertälje Sweden	+46 8 553 288 20		
- Sweden	Teleprinter No.		
Mark this check-box where no agent or common representa	tive is/has been appointed and the space above is used instead to		
indicate a special address to which correspondence should be	See Motor to the request form		

Sheet No. 2

Continuation of Box No. III FURTHER APPLICANTS AN	D/OR (FURTHER) INVENTORS
If none of the following sub-boxes is used, t	his sheet is not to be included in the request.
Name and address: (Family name followed by given name: for a legal entitle address must include postal code and name of country. The country of Box is the applicant's State (i.e. country) of residence if no State of residence SOHN, Daniel D Astra Arcus AB S-151 85 Södertälje Sweden	ity, full official designation. the address indicated in this applicant only  This person is:  applicant only  applicant and inventor  inventor only (If this check-box is marked, do not fill in below.)
State (i.e. as well of notionality)	State (i.e. annum) of residence:
State (i.e. country) of nationality: US	State (i.e. country) of residence:  SE
This person is applicant all designated for the purposes of:  all designated the United States all designated the United States	States except the United States the States indicated in the Supplemental Box
Name and address: (Family name followed by given name, for a legal ent The address must include postal code and name of country. The country of t Box is the applicant's State (i.e. country) of residence if no State of residence	ity, full official designation. the address indicated in this see is indicated below.)  This person is:  applicant only  applicant and inventor  inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant all designated all designated for the purposes of: States the United State	States except the United States the States indicated in the Supplemental Box
Name and address: (Family name followed by given name; for a legal ent The address must include postal code and name of country. The country of t Box is the applicant's State (i.e. country) of residence if no State of residence	iry, full official designation. the address indicated in this see is indicated below.)  This person is:  applicant only  applicant and inventor  inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant all designated all designated for the purposes of:	States except the United States the States indicated in the Supplemental Box
Name and address: (Family name followed by given name; for a legal ent The address must include postal code and name of country. The country of the Box is the applicant's State (i.e. country) of residence if no State of residence	ity, full official designation. the address indicated in this e is indicated below.)  This person is:  applicant only  applicant and inventor  inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant all designated all designated for the purposes of States the United Sta	States except the United States the States indicated in the sof America only the Supplemental Box
for the purposes of: States the United Sta	

Box N	lo.V	DESIGNATION OF STATES					
The fo	ollowi	ng designations are hereby made under Rule 4.9(a) (m	ark the	e appli	cable check-boxes; at least one must be marked):		
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X	AP	ARIPO Patent: GH Ghana, GM Gambia, KE Keny	a, LS	Lesoth	no, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda,		
		ZW Zimbabwe, and any other State which is a Con-	tractin	g Stat	e of the Harare Protocol and of the PCT		
X	EA	Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT.					
X	ED	of the Eurasian Patent Convention and of the PCT			zerland and Liechtenstein, <b>DE</b> Germany, <b>DK</b> Denmark,		
NO.	EP	ES Spain, FI Finland, FR France, GB United Kingdo	om, Gl	R Gree	ece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, e which is a Contracting State of the European Patent		
X	OA	OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)					
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X	ES	Spain	X	SG	Singapore		
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X		Gambia	X		Turkmenistan		
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In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

LR Liberia

Sheet No. 4....

Box No. VI	PRIORITY CI	LAIM	F	urther priority clai	ms are indicat	ed in the Supplemental Box
The priority of	the following ea	rlier application	(s) is hereby claim	ied:	<del> </del>	
Cou (in which, or application	untry for which, the was filed)		ng Date onth/year)	Applic	cation No.	Office of filing (only for regional or international application)
tem(1) Sweden		30 May 199 (30.05.1997		9702066-3		
tem(2)		(30.00.100.	,	0,02000		
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pplication is the	receiving Office (a eiving Office is h	fee may be required ereby requested t	l): to prepare and trar	is to be issued by the (asmit to the Internaled above as item(s)	tional	the purposes of the present international
Box No. VII	INTERNATIO	NAL SEARCH	ING AUTHORI	ГҮ		
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Sweden		22 Se	ptember 1997	(22.09.1997)	173	S SE 97/00696
Box No. VIII	CHECK LIST				· · · · · · · · · · · · · · · · · · ·	
	ational application at a position at a posit		1. separa	nal application is ac ate signed r of attorney		the item(s) marked below: fee calculation sheet
2. descri 3. claims	•	sheets sheets	2. <b>x</b> copy opower	of general r of attorney	6.	separate indications concerning deposited microorganisms
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Figure No. 2	of the	drawings (if any	) should accompa	ny the abstract wh	en it is publish	ned.
Box No. IX	SIGNATURE	OF APPLICAN	T OR AGENT			· · · · · · · · · · · · · · · · · · ·
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